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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/507,239	02/18/2000	Hugh S. Keeping	04930-028001	9324

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 04/09/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/507,239

Applicant(s)

Keeping

Examiner

Anne Marie Wehbé

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jan 30, 2003
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38-49 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 15 6) ☐ Other:

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DETAILED ACTION

Applicant's amendment and response received on 1/30/03 has been entered. Claims 50-59 have been cancelled and claims 38 and 43 amended. Claims 38-49 are pending in the instant application. Please note that although the applicant states that a claim 60 is also pending, no claim 60 presently exists in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in previous office actions.

Claim Rejections - 35 USC § 102

The rejection of claims 38, 39, 42-44, 47-49 under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al. (1996) Biochem. Biophys. Res. Comm., Vol. 220, 366-371, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 38-49 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,281,195 (8/28/01), hereafter referred to as Rueger et al., in view of Yamaguchi et al.

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(1996) Biochem. Biophys. Res. Comm., Vol. 220, 366-371. is withdrawn in view of applicant's amendments to the claims.

Applicant's amendment have necessitated the following new grounds of rejection.

Claims 38-49 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (1996) Biochem. Biophys. Res. Comm., Vol. 220, 366-371 in view of Lecanda et al. (1997) J. Cell. Biochem., Vol. 67, 386-398, and further in view of U.S. Patent No. 6,281,195 (8/28/01), hereafter referred to as Rueger et al., U.S. Patent No. 5,830,708 (11/3/98), hereafter referred to as Naughton et al., and Reddi, A. M. (1995) Clin. Ortho. Rel. Res., Vol. 313, 115-119. The applicant claims a method of inducing the differentiation of an isolated bone marrow stromal cell comprising contacting the cell *ex vivo* with bone morphogenetic protein 2, 4, or 6 and an extracellular matrix, wherein the cell is isolated from a bone marrow aspirate. The applicant further claims said method wherein the cells are human, or canine cells, and wherein the BMP is BMP-6.

Yamaguchi et al. teaches the differentiation of murine bone marrow stromal cells comprising contacting the cells during *in vitro* tissue culture with human bone morphogenetic protein (BMP) 2, or BMP-4, or BMP-6 (Yamaguchi et al., page 366, abstract, and page 369, Figure 3). Yamaguchi et al. further teaches that the cell used in these experiments were obtained from the RIKEN Cell Bank in Tsukuba, Japan. At the time of filing, it was well known that cell

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lines are stored by freezing the cells in liquid nitrogen. Frozen cell lines are capable of being shipped around and subsequently thawed at the destination for use in biological assays. Thus, by using a cell line obtained from a cell bank, Yamaguchi et al. teaches the use of cells which have been previously frozen.

Although Yamaguchi et al. teaches that bone marrow stromal cells differentiate in response to BMPs, including BMP-2 and BMP-6 in tissue culture, Yamaguchi et al. does not specifically teach the use of bone marrow stromal cells isolated from bone marrow aspirate. Lecanda et al. supplements Yamaguchi et al. by teaching that human bone marrow stromal cells isolated from bone marrow aspirate are also capable of differentiating in response to BMPs, and specifically BMP-2 (Lecanda et al., page 388, column 1, and page 396). Thus, based on the teachings of Lecanda et al. that isolated bone marrow stromal cells are equally susceptible to BMP induced differentiation, it would have been *prima facie* obvious to the skilled artisan at the time of filing to differentiate bone marrow stromal cells from different sources by contacting the cells *ex vivo/in vitro* with BMPs, especially BMP-2 and BMP-6. Further, based on the successful demonstrations by both Yamaguchi and Lecanda that BMPs induce bone marrow stromal cell differentiation, the skilled artisan would have had a reasonable expectation of success in inducing the differentiation of bone marrow stromal cells from different sources, i.e. from bone marrow aspirate or from a thawed cell line sample, by contacting the cells *ex vivo/in vitro* with BMPs, especially BMP-2 and BMP-6.

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Yamaguchi et al. teaches murine bone marrow stromal cells and Lecanda et al. teaches human bone marrow stromal cells. Rueger et al. supplements the teachings of Yamaguchi et al. and Lecanda et al. by teaching methods of inducing bone formation in a mammal comprising providing directly to the defect locus in a bone an osteogenic protein such as BMP-2, BMP-4, or BMP-6 (Rueger et al., columns 54-55, claims 1, 11 and 12). While Rueger et al. does not specifically state that the osteogenic protein comes in contact with bone marrow stromal cells, it was well known at the time of filing that bone marrow contains bone marrow stromal cells, as evidenced by Lecanda. Rueger et al. further teaches that the osteogenic protein can be administered to numerous types of mammals including dogs, rabbits, and humans (Rueger et al., columns 3-4, and columns 25-30). Based on the teachings of Rueger et al., that BMP-2, BMP-4, and BMP-6 are capable of inducing the differentiation of bone marrow stromal cells in many types of mammals including dogs as well as humans, it would have been *prima facie* obvious to the skilled artisan at the time of filing to differentiate bone marrow stromal cells from any mammalian source by culturing the cells according to the methods disclosed by Yamaguchi et al. and Lecanda et al. with a reasonable expectation of success.

Yamaguchi et al. and Lecanda et al. both differ from the instant invention by failing to teach the inclusion of an extracellular matrix in the bone marrow stromal cell cultures. Naughton et al. supplements Yamaguchi et al. and Lecanda et al. by teaching methods of producing extracellular matrix material for use in cell culture *in vitro* (Naughton et al., columns 17-18, and column 4, lines 6-18). Reddi provides motivation for adding the extracellular matrix taught by

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Naughton et al. to the *in vitro* cultures taught by Yamaguchi et al. and Lecanda et al. by teaching that terminal differentiation of osteogenic cells occurs as a result of the combined effects of extracellular matrix and bone morphogenetic proteins (Reddi, abstract, page 115). Based on the motivation provided by Reddi that extracellular matrix combines with BMPs to induce terminal differentiation of osteogenic precursor cells, it would have been *prima facie* to the skilled artisan to add extracellular matrix and produced according to Naughton et al. to the cultures of bone marrow stromal cells taught by Yamaguchi et al. and Lecanda et al.. Further, based on the known collaborative effects of BMPs and extracellular matrix on osteogenic precursor cell differentiation, the skilled artisan would have had a reasonable expectation of success in inducing the differentiation of isolated bone marrow stromal cells by culturing the cells *ex vivo/in vitro* with BMPs, specifically BMP-2 and BMP-6, and extracellular matrix.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the

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THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

